Heyde Syndrome: Resolution of Anemia after Aortic Valve Surgery

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Heyde syndrome was first described in 1958 by Dr. Edward C. Heyde as the combination of calcified aortic stenosis and gastrointestinal bleeding. Today this syndrome is recognized as a triad of severe aortic stenosis, angiodysplasia of the gastrointestinal tract, and acquired von Willebrand syndrome type 2A [1,2]. Many questions regarding its pathophysiology and treatment remain unanswered. We present a case of severe gastrointestinal bleeding from angiodysplasia associated with severe aortic stenosis that severely compromised the quality of life of this patient but resolved after aortic valve replacement.

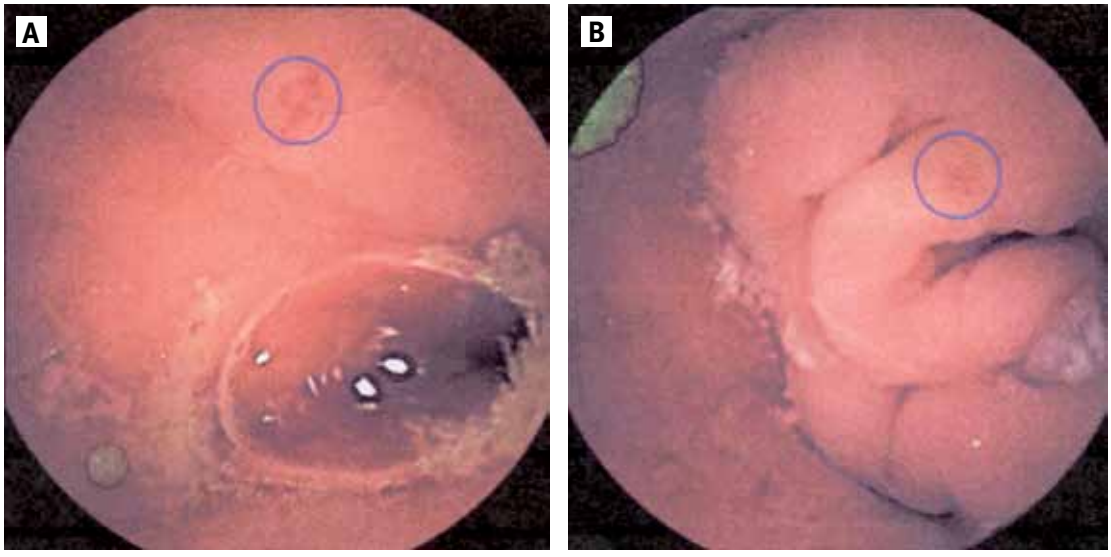
PATIENT DESCRIPTION

A 76 year old woman first attended our primary clinic in 2007. Her medical history revealed childhood polio with spastic paresis of her legs, primary biliary cirrhosis since 1998 with fibrosis grade II-III and stable normal liver function, hypertension, and a stable-size mild abdominal aortic aneurysm (3.2 cm). She had a calcified aortic valve with moderate stenosis estimated at a 60 mmHg gradient with a valve area of 1.2 cm^2. In January 2007 the patient experienced severe weakness and a blood count revealed anemia with hemoglobin 9.4 mg/dl. She was admitted to the hospital, and gastroscopy and colonoscopy, as well as small intestine barium study were normal. Bone marrow was normal. Later, using the intestinal capsule, angiodysplasia was detected in the duodenum [Figures A & B].

Between the years 2007 and 2010 the patient suffered from chronic symptomatic anemia with recurrent episodes of melena and hematochezia. Her hemoglobin dropped to 7 mg/dl. She was admitted to the hospital seven times, underwent colonoscopy three times, received two packed red blood cells four times and intravenous parenteral iron once weekly, and was treated by enteroscopy with argon coagulation four times. Despite this treatment, her hemoglobin was still low, around 9 mg/dl.

The hepatologist denied any connection with her hepatic condition, and her coagulation tests were normal. An echocardiography study in 2010 demonstrated

Angioectasias (in blue circle) in the proximal duodenum as seen in the capsule endoscopy performed in October 2008. Two pictures from the same study showing atriovenous malformation after 40 **[A]** and 50 **[B]** minutes respectively



severe aortic stenosis, aortic valve area 0.8 cm², and peak pressure gradient 68 mmHg.

A literature search raised the possibility of Heyde syndrome, suggesting that repair of her aortic valve may ameliorate her chronic suffering and improve her quality of life. In January 2010 cardiac catheterization demonstrated severe triple vessel disease as well as severe aortic stenosis. A successful coronary bypass graft surgery and biological aortic valve replacement were performed.

For the last 3½ years since the surgery her hemoglobin remains stable, above 11 mg/dl, although she experienced two episodes of a hemoglobin drop to 9.6 mg/dl. During that period she was not hospitalized, did not receive any blood transfusion and did not undergo any invasive procedure.

COMMENT

Heyde syndrome is the association between calcific aortic stenosis, GI bleeding due to angiodysplasia and acquired von Willebrand syndrome type 2A. In aortic stenosis the mechanism is thought to involve mechanical disruption of large von Willebrand factor multimers from shear stress during turbulent passage through the narrowed valve. Exposure to shear stress causes a change in shape from a coiled structure to an elongated filament and exposes it to specific protease activity [2,3]. A similar phenomenon has also been described in other high shear stress conditions such as hypertrophic obstructive cardiomyopathy, supravalvular aortic stenosis, ventricular septal defect and patent ductus arteriosus. The large multimers are important for hemostasis as they mediate platelet adhesion to the vessel wall in situations of high velocity blood flow. Angiodysplastic vessels themselves are associated with high velocity blood flow. Therefore, a lack of large multimers would be expected to prolong bleeding from these vessels. Thus, patients with von Willebrand syndrome type 2A due to aortic stenosis may be more likely to bleed from existing angiodysplasia [2].

Aortic stenosis is the most common acquired valvular lesion in the elderly. The prevalence of critical aortic stenosis is 1%–2% at age 75, rising to 6% at 85 years. The precipitating cause is unknown, but chronic inflammation of the valves causing thickening and fusion of the aortic valve cusps and calcification seems plausible [2-4].

Risk factors for aortic stenosis are similar to those for arterial atherosclerosis. Critical disease may present with syncope, angina and dyspnea [2]. Angiodysplasia may occur anywhere in the GI tract but is most common in the ascending colon, particularly the cecum. In a prospective study of colonoscopies in 1938 patients, typical angiodysplasia was found in 3% of cases but 80% were asymptomatic. The sites of the highest prevalence of lesions were the cecum (37%) and sigmoid colon (18%). Around 30–40% of GI bleeds from an obscure source were found to be linked to angiodysplasia, which is possibly the most common cause of lower gastrointestinal bleeding in the elderly [5].

In their retrospective study of 3.8 million discharge summaries, Pate and colleagues [2] found a significant association ($P < 0.0001$) between aortic stenosis and GI bleeding presumed to be due to angiodysplasia. Age was statistically significant as a confounding factor, as patients who had been diagnosed with both conditions were older than patients with only one or neither ($P < 0.0001$) [2]. Shoenfeld et al. [4] found an association between GI bleeding and aortic stenosis but not with mitral stenosis [4].

In an elderly patient with established aortic stenosis, development of iron deficiency anemia should raise the possibility of Heyde syndrome. Initial investigations should explore other possibilities such as underlying gastrointestinal malignancy, celiac disease or nutritional deficiency. The presence of angiodysplasia on sigmoidoscopy or colonoscopy, or a failure of the investigations to find any clear site of GI bleeding, should raise the possibility of Heyde syndrome. For patients in whom initial investigations show no abnormality, angiodysplasia may be diagnosed by capsule endoscopy

In von-Willebrand syndrome type 2A, routine screening tests for vWF are usually normal. The gold standard is gel electrophoresis of vWF, although it is costly and resource intensive [2,5]. Routine laboratory tests performed for von Willebrand disease, such as vWF antigen levels and ristocetin cofactor activity, are often normal in this syndrome. The sensitivity of various tests for acquired von Willebrand deficiency has been ranked as follows: gel electrophoresis (most sensitive), Platelet Function Analyzer-100 closure time, skin bleeding time, vWF ristocetin cofactor activity, and vWF antigen level (least sensitive). However, an echocardiogram might be considered in any older patient with obscure or recurrent GI bleed to rule out aortic stenosis as the cause [2,5].

Despite the unresolved question whether aortic valve replacement may stop gastrointestinal bleeding, replacement of the stenotic valve, rather than resection of the affected bowel tract, provides the most effective treatment [1-3]. Surgical resection of the affected portion of intestine is often followed by recurrence of symptoms from previously latent disease in other segments [1,2,5].

In a study of 50 consecutive patients with aortic stenosis, cutaneous or mucosal bleeding occurred in 21% of patients and hematological abnormalities, which correlated with the severity of the stenosis, in 67–92%. In this cohort, 42 patients (84%) had surgical treatment (11 mechanical bileaflet prosthetic device and 31 biological device) and 38 patients were asymptomatic at 6 months follow-up (one had early homograft stenosis and the others were lost to follow-up) [3]. A retrospective review at the Mayo Clinic identified 57 patients with Heyde syndrome who underwent aortic valve replacement. During follow-up extending to 15 years, 45 patients (79%)

GI = gastrointestinal

vWF = von Willebrand factor

had no recurrence of bleeding. In patients who experienced recurrent bleeding, the episodes were reduced. Among patients who received bioprostheses, the overall risk of recurrent bleeding was 15%, which was lower than the 50% risk of subsequent gastrointestinal bleeding with mechanical prostheses, making the bioprostheses the valve of choice for most patients [1].

Patients presenting with gastrointestinal bleeding of unknown origin should be examined carefully for aortic stenosis. Echocardiography should be performed in patients with normal colonoscopies or proven arteriovenous malformations. The management of patients with severe aortic stenosis and gastrointestinal bleeding is complex. These patients almost always require endoscopic procedures, including colonoscopy and esophagogastroduodenoscopy. Management of this syndrome often requires the cooperation of the family physician, cardiologists, gastroenterologists, hematologists and surgeons.

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Capsule

Delaying embryo implantation in mammals

Many mammals can delay embryo implantation in order to postpone pregnancy when conditions are unfavorable, or until later birthing seasons. Such embryonic diapause occurs when development is suspended in the blastocyst stage and implantation is prevented. Endocrine factors trigger diapause, but the mechanism coordinating blastocyst dormancy and uterine quiescence remains unknown. Cha et al. show that the gene *Msx1* is expressed when implantation is delayed, whether it occurs because of maternal lactation, ovariectomy, or the addition of antiestrogen. When implantation initiates, *Msx1* expression is down-regulated. Further, genetic inactivation of *Msx1* or *Msx2* in the uterus results in the development of fewer blastocysts. In order for delayed implantation to occur, blastocyst dormancy must coincide with uterine quiescence. This work demonstrates a critical role of *Msx1* in maternal regulation of embryonic diapause. The study finds that three distantly related mammalian orders – Rodentia (mouse), Carnivora (American mink), and Diprotodontia (Australian tammar wallaby) – display correlations between Msx expression and diapause, suggesting the presence of a conserved reproductive strategy across mammalian species.

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Capsule

Intestinal microbiota metabolism of l-carnitine, a nutrient in red meat, promotes atherosclerosis

Intestinal microbiota metabolism of choline and phosphatidylcholine produces trimethylamine (TMA), which is further metabolized to a pro-atherogenic species, trimethylamine-*N*-oxide (TMAO). Koeth et al. demonstrate that metabolism by intestinal microbiota of dietary l-carnitine, a trimethylamine abundant in red meat, also produces TMAO and accelerates atherosclerosis in mice. Omnivorous human subjects produced more TMAO than did vegans or vegetarians following ingestion of l-carnitine through a microbiota-dependent mechanism. The presence of specific bacterial taxa in human feces was associated with both plasma TMAO concentration and dietary status. Plasma l-carnitine levels in subjects undergoing cardiac evaluation (n=2595) predicted increased risks for both prevalent cardiovascular disease (CVD) and incident major adverse cardiac events (myocardial infarction, stroke or death), but only among subjects with concurrently high TMAO levels. Chronic dietary l-carnitine supplementation in mice altered cecal microbial composition, markedly enhanced synthesis of TMA and TMAO, and increased atherosclerosis, but this did not occur if intestinal microbiota was concurrently suppressed. In mice with an intact intestinal microbiota, dietary supplementation with TMAO or either carnitine or choline reduced in vivo reverse cholesterol transport. Intestinal microbiota may thus contribute to the well-established link between high levels of red meat consumption and CVD risk.

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